PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
A61K 31/198, 9/20, 9/36

A1

(11) International Publication Number: **WO 00/59500**

(43) International Publication Date: 12 October 2000 (12.10.00)

(21) International Application Number: PCT/EP00/02464

(22) International Filing Date: 21 March 2000 (21.03.00)

(30) Priority Data:
MI99A000704 6 April 1999 (06.04.99) IT

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(81) Designated States: AU, BR, CA, CN, HU, IL, JP, MX, NZ, US, ZA, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: SWALLOWABLE TABLETS WITH HIGH CONTENT OF N–ACETYLCYSTEINE

(57) Abstract

A swallowable tablet containing 80–95 % N–acetylcysteine by weight, 0.5–4 % by weight with respect to N–acetylcysteine of a binder and further pharmaceutically acceptable excipients, such as diluents, disintegrants, lubricants, optionally in the presence of a flowing agent and of a film–coating layer, is described.

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Swallowable tablets with high content of N-acetylcysteine

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The present invention relates to swallowable tablets with high content of N-acetylcysteine.

N-acetylcysteine (NAC) is a compound known for time and mainly used in therapy as mucolytic and expectorant (The Merck Index, XII ed., page 16, no. 89).

Usually NAC is administered by topical route or by oral route in the form of a granulate or tablet.

For the oral solid administration, presently NAC is formulated only at the maximum dose of 200 mg in chewable tablets to be dissolved in the mouth. This implies the need to mask the taste as well as the smell of this active ingredient, known to be not very pleasant because of the presence of a sulphur group in the molecule.

Just for the need to use a high number and amount of excipients to mask the taste and the smell, there are on the market neither oral NAC formulations containing more than 65% by weight of active ingredient nor NAC formulations as swallowable tablets with a dose higher than 200 mg/tablet.

The formulation of tablets for the oral administration containing a high percentage of active ingredient is generally difficult.

US patent 4,908,210 (Eastman Kodak Company) claims a compressible powder containing 0.5-5% by weight of a specific mixture of lubricants (monoglycerides, propylene-glycol monoesters, a salt of a fatty acid ester of lactic acid) so to give finished tablets containing a percentage of active ingredient higher than 80%. Such a powder shows economic drawbacks since some excipients of the lubricant mixture are particularly expensive.

US patent 5,501,861 (Takeda Chemical Industry Ltd) illustrates fast dissolving tablets containing the active ingredient in the percentage of 0.05-90% by weight of the semifinished product and a hydrosoluble carbohydrate in a percentage of 30-80% by weight. However, this document underlines that the use of 30-70% by weight of active ingredient is preferred to obtain a tablet with a high dosage. In fact, the examples of final formulation never contain percentages of active ingredient higher than 50%.

US patent 5,401,514 (Spirig AG) claims an oral solid formulation of at least 50% NAC or carboxy-methyl-cysteine by weight in admixture with at least a cellulose, a soluble sugar, a

sweetener and a flavour. The same formulation is claimed with a NAC content of 100 mg and 200 mg. The content of active ingredient in the exemplified formulations reaches 65% by weight at the maximum.

A swallowable tablet with a high content of NAC has been now found.

Therefore, the present invention relates to a swallowable tablet containing 80-95% NAC by weight, 0.5-4% by weight with respect to NAC of a binder and further pharmaceutically acceptable excipients.

Preferably, the swallowable tablet object of the present invention contains 80-95% NAC by weight, 1-3% binder by weight, 2.5-14% diluent by weight, 1-4.5% disintegrant by weight, 0.1-1.5% lubricant by weight, optionally in the presence of a flowing agent and of a film-coating layer.

Still more preferably, the swallowable tablet object of the present invention contains 80-90% NAC by weight, 2-3% binder by weight, 3-14% diluent by weight, 1-4.5% disintegrant by weight, 0.1-1% lubricant by weight, 0.1-1% flowing agent and optionally a film-coating layer equal to or lower than 4% by weight.

Examples of binders according to the present invention are linear polyvinylpyrrolidone, sodium carboxymethylcellulose, ethylcellulose, methylcellulose, liquid glucose, gelatine and hydroxypropylcellulose.

Preferably linear polyvinylpirrolidone is used.

Examples of lubricants according to the present invention are magnesium stearate, sodium stearyl fumarate, sodium benzoate and polyethylene glycol.

Magnesium stearate is preferably used.

Examples of diluents according to the present invention are carbohydrates, such as lactose and saccharose, microcrystalline cellulose and derivatives thereof, inorganic salts, such as dibasic calcium phosphate and sodium bicarbonate, polyalcohols, such as sorbitol, mannitol and xylitol, and mixtures thereof.

Microcrystalline cellulose and its derivatives or mixtures thereof are preferably used.

Examples of disintegrants according to the present invention are cross-linked polyvinylpyrrolidone, sodium croscarmellose, sodium carboxymethyl starch, starch,

pregelatinized starch and microcrystalline cellulose.

Cross-linked polyvinylpyrrolidone and sodium croscarmellose are preferably used.

When present, the preferably used flowing agent is colloidal silica.

The tablet object of the invention is prepared by wet granulation of the active ingredient with a binder and optionally all or part of the estimated amount of diluent and/or of the lubricant. The granulate is then mixed and compressed with the other excipients and the resultant tablet optionally undergoes a film-coating procedure.

This optional film-coating is carried out according to conventional techniques by preferably using cellulose acetate phthalate, ethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose and metacrylic acid co-polymers, as coating agents, in admixture with opacifiers, plasticizers and, optionally, dyes and sweetening agents.

Preferably the preparation of the swallowable tablet object of the present invention is carried out by wet granulation of NAC with a binder. The resultant granulate is then mixed with the remaining excipients and compressed.

The use of such a low amount of excipients makes possible the preparation of swallowable tablets containing a high dose of NAC, while keeping the final size of the tablet within acceptable values, that is suitable for the swallowing.

A particularly preferred feature of the present invention is therefore represented by the preparation of tablets containing a dose of NAC equal to or higher than 400 mg, more preferably equal to 600 mg.

The tablets containing 600 mg NAC, according to the present invention, have a weight from 630 mg to 750 mg. For the preparation of tablets having this weight, conventional moulds such as, for example, convex tablets with 12-mm diameter or capsule-shaped tablets with sizes 18.16 x 7.41 mm, commonly used for swallowable tablets, can be used.

Furthermore, the tablets object of the present invention show physical characteristics which fulfil the requirements imposed by the Official Pharmacopoeias.

For example, the hardness of the tablets will be generally from 6 to 14 Kp, the friability from 0.05 to 0.7% and the disintegration time lower than 15 minutes for the non-film coated tablets.

In order to better illustrate the present invention the following examples are now given.

Example 1

Preparation of the granulates

By using a wet granulation procedure in a rotogranulator, the following granulates were prepared (% by weight):

	GRANULATE							
	A	B	C	D	E	F	G	H
NAC	97%	98%	89%	90%	89%	90%	96%	89%
PVP K30	3%	2%	3%	2%	3%	2%	3%	2%
lactose	----	----	8%	8%	----	----	----	8%
mannitol	----	----	----	----	8%	8%	----	----
PEG 6000	----	----	----	----	----	----	1%	1%

The granulates (2 Kg each batch) were dried, screened and used for the preparation of the tablets according to what reported in the following examples.

Example 2

Granulate A (2 Kg) was mixed with microcrystalline cellulose, sodium bicarbonate, PVP CL and magnesium stearate. The mixture was compressed to obtain tablets having the following composition expressed as mg/tablet (% by weight):

NAC	600.0 mg	(84.4%)
PVP K30	18.0 mg	(2.5%)
microcrystalline cellulose	50.8 mg	(7.1%)
sodium bicarbonate	20.0 mg	(2.8%)
PVP CL	16.0 mg	(2.3%)
magnesium stearate	6.2 mg	(0.9%)
total weight	711.0 mg	

Example 3

Granulate A (2 Kg) was mixed with microcrystalline cellulose, PVP CL and magnesium stearate. The mixture was compressed to obtain tablets having the following composition expressed as mg/tablet (% by weight):

NAC	600.0 mg	(83.8%)

PVP K30	18.0 mg	(2.5%)
microcrystalline cellulose	75.8 mg	(10.6%)
PVP CL	16.0 mg	(2.2%)
magnesium stearate	6.2 mg	(0.9%)
total weight	716.0 mg	

Example 4

Granulate A (2 Kg) was mixed with microcrystalline cellulose, PVP CL, magnesium stearate and colloidal silica. The mixture was compressed to obtain tablets having the following composition expressed as mg/tablet (% by weight):

NAC	600.0 mg	(83.9%)
PVP K30	18.0 mg	(2.5%)
microcrystalline cellulose	60.0 mg	(8.4%)
PVP CL	30.0 mg	(4.2%)
magnesium stearate	3.5 mg	(0.5%)
colloidal silica	3.5 mg	(0.5%)
total weight	715.0 mg	

Example 5

Granulate A (2 Kg) was mixed with dibasic calcium phosphate, PVP CL, magnesium stearate and colloidal silica. The mixture was compressed to obtain tablets having the following composition expressed as mg/tablet (% by weight):

NAC	600.0 mg	(83.8%)
PVP K30	18.0 mg	(2.5%)
dibasic calcium phosphate	60.8 mg	(8.5%)
PVP CL	30.0 mg	(4.2%)
magnesium stearate	3.6 mg	(0.5%)
colloidal silica	3.6 mg	(0.5%)
total weight	716.0 mg	

Example 6

Granulate A (2 Kg) was mixed with lactose, PVP CL, magnesium stearate and colloidal

silica. The mixture was compressed to obtain tablets having the following composition expressed as mg/tablet (% by weight):

NAC	600.0 mg	(83.33%)
PVP K30	18.0 mg	(2.50%)
lactose	75.0 mg	(10.42%)
PVP CL	16.0 mg	(2.22%)
magnesium stearate	6.4 mg	(0.89%)
colloidal silica	4.6 mg	(0.64%)
total weight	720.0 mg	

Example 7

Granulate A (2 Kg) was mixed with microcrystalline cellulose, sodium croscarmellose and magnesium stearate. The mixture was compressed to obtain tablets having the following composition expressed as mg/tablet (% by weight):

NAC	600.0 mg	(85.7%)
PVP K30	18.0 mg	(2.6%)
microcrystalline cellulose	45.8 mg	(6.5%)
sodium croscarmellose	30.0 mg	(4.3%)
magnesium stearate	6.2 mg	(0.9%)
total weight	700.0 mg	

Example 8

Granulate A (2 Kg) was mixed with microcrystalline cellulose, PVP CL and magnesium stearate. The mixture was compressed to obtain tablets having the following composition expressed as mg/tablet (% by weight):

NAC	600.0 mg	(85.7%)
PVP K30	18.0 mg	(2.6%)
microcrystalline cellulose	45.8 mg	(6.5%)
PVP CL	30.0 mg	(4.3%)
magnesium stearate	6.2 mg	(0.9%)
total weight	700.0 mg	

Example 9

Granulate C (2 Kg) was mixed with PVP CL, magnesium stearate and colloidal silica. The mixture was compressed to obtain tablets having the following composition expressed as mg/tablet (% by weight).

NAC	600.0 mg	(84.4%)
PVP K30	20.0 mg	(2.8%)
lactose	54.0 mg	(7.6%)
PVP CL	30.0 mg	(4.2%)
magnesium stearate	4.0 mg	(0.6%)
colloidal silica	3.0 mg	(0.4%)
total weight	711.0 mg	

Example 10

Granulate D (2 Kg) was mixed with microcrystalline cellulose, PVP CL, magnesium stearate and colloidal silica. The mixture was compressed to obtain tablets having the following composition expressed as mg/tablet (% by weight):

NAC	600.0 mg	(82.6%)
PVP K30	15.0 mg	(2.1%)
lactose	54.0 mg	(7.4%)
microcrystalline cellulose	30.0 mg	(4.1%)
PVP CL	20.0 mg	(2.8%)
magnesium stearate	4.0 mg	(0.6%)
colloidal silica	3.0 mg	(0.4%)
total weight	726.0 mg	

Example 11

Granulate E (2 Kg) was mixed with microcrystalline cellulose, PVP CL, magnesium stearate and colloidal silica. The mixture was compressed to obtain tablets having the following composition expressed as mg/tablet (% by weight):

NAC	600.0 mg	(81.52%)
PVP K30	20.0 mg	(2.72%)

mannitol	54.0 mg	(7.34%)
microcrystalline cellulose	30.0 mg	(4.08%)
PVP CL	25.0 mg	(3.40%)
magnesium stearate	4.0 mg	(0.54%)
colloidal silica	3.0 mg	(0.40%)
total weight	736.0 mg	

Example 12

Granulate F (2 Kg) was mixed with dibasic calcium phosphate, PVP CL, magnesium stearate and colloidal silica. The mixture was compressed to obtain tablets having the following composition expressed as mg/tablet (% by weight):

NAC	600.0 mg	(81.52%)
PVP K30	15.0 mg	(2.04%)
mannitol	54.0 mg	(7.34%)
dibasic calcium phosphate	40.0 mg	(5.44%)
PVP CL	20.0 mg	(2.72%)
magnesium stearate	4.0 mg	(0.54%)
colloidal silica	3.0 mg	(0.40%)
total weight	736.0 mg	

Example 13

Granulate G (2 Kg) was mixed with microcrystalline cellulose, sodium bicarbonate, PVP CL and magnesium stearate. The mixture was compressed to obtain tablets having the following composition expressed as mg/tablet (% by weight):

NAC	600.0 mg	(84.39%)
PVP K30	18.0 mg	(2.53%)
PEG 6000	6.0 mg	(0.84%)
microcrystalline cellulose	50.8 mg	(7.15%)
sodium bicarbonate	14.0 mg	(1.97%)
PVP CL	16.0 mg	(2.25%)
magnesium stearate	6.2 mg	(0.87%)

total weight	711.0 mg	

Example 14

Granulate G (2 Kg) was mixed with microcrystalline cellulose, colloidal silica, PVP CL and magnesium stearate. The mixture was compressed to obtain tablets having the following composition expressed as mg/tablet (% by weight):

NAC	600.0 mg	(83.22%)
PVP K30	18.0 mg	(2.49%)
PEG 6000	6.0 mg	(0.83%)
PVP CL	30.0 mg	(4.16%)
microcrystalline cellulose	60.0 mg	(8.32%)
colloidal silica	3.5 mg	(0.49%)
magnesium stearate	3.5 mg	(0.49%)
total weight	721.0 mg	

Example 15

Granulate G (2 Kg) was mixed with microcrystalline cellulose, colloidal silica, PVP CL and magnesium stearate. The mixture was compressed to obtain tablets having the following composition expressed as mg/tablet (% by weight):

NAC	400.0 mg	(83.22%)
PVP K30	12.0 mg	(2.49%)
PEG 6000	4.0 mg	(0.83%)
PVP CL	20.0 mg	(4.16%)
microcrystalline cellulose	40.0 mg	(8.32%)
colloidal silica	2.33 mg	(0.49%)
magnesium stearate	2.33 mg	(0.49%)
total weight	480.66 mg	

Example 16

Granulate G (2 Kg) was mixed with microcrystalline cellulose, colloidal silica, PVP CL and magnesium stearate. The mixture was compressed to obtain tablets having the following composition expressed as mg/tablet (% by weight):

NAC	200.0 mg	(83.22%)
PVP K30	6.0 mg	(2.49%)
PEG 6000	2.0 mg	(0.83%)
PVP CL	10.0 mg	(4.16%)
microcrystalline cellulose	20.0 mg	(8.32%)
colloidal silica	1.16 mg	(0.49%)
magnesium stearate	1.16 mg	(0.49%)
total weight	240.32 mg	

Example 17

Granulate A (2 Kg) was mixed with PVP CL, microcrystalline cellulose, colloidal silica and magnesium stearate. The mixture was compressed to obtain tablets having the following composition expressed as mg/tablet (% by weight):

NAC	400.0 mg	(83.92%)
PVP K30	12.0 mg	(2.52%)
PVP CL	20.0 mg	(4.19%)
microcrystalline cellulose	40.0 mg	(8.39%)
colloidal silica	2.33 mg	(0.49%)
magnesium stearate	2.33 mg	(0.49%)
total weight	476.66 mg	

Example 18

Granulate A (2 Kg) was mixed with PVP CL, microcrystalline cellulose, colloidal silica and magnesium stearate. The mixture was compressed to obtain tablets having the following composition expressed as mg/tablet (% by weight):

NAC	200.0 mg	(83.92%)
PVP K30	6.0 mg	(2.52%)
PVP CL	10.0 mg	(4.19%)
microcrystalline cellulose	20.0 mg	(8.39%)
colloidal silica	1.16 mg	(0.49%)
magnesium stearate	1.16 mg	(0.49%)

total weight	238.32 mg	

Example 19

The tablets prepared as described in example 4 were coated with a mixture of hydroxypropylmethylcellulose, titanium dioxide and PEG 6000.

The mixture was suspended in water (suspension at 10-15%) and sprayed into a coating pan.

The resultant film-coated tablets have the following composition expressed as mg/tablet (% by weight):

NAC	600.0 mg	(82.4%)
PVP K30	18.0 mg	(2.5%)
microcrystalline cellulose	60.0 mg	(8.2%)
PVP CL	30.0 mg	(4.1%)
magnesium stearate	3.5 mg	(0.5%)
colloidal silica	3.5 mg	(0.5%)
HPMC	5.0 mg	(0.7%)
titanium dioxide	5.0 mg	(0.7%)
PEG 6000	3.0 mg	(0.4%)
total weight	728.0 mg	

Example 20

The tablets prepared as described in example 4 were coated with a mixture of metacrylic acid copolymer, titanium dioxide and polysorbate 80.

The mixture was suspended in water (suspension at 10-15%) and sprayed into a coating ban.

The resultant film-coated tablets have the following composition expressed as mg/tablet (% by weight):

NAC	600.0 mg	(82.27%)
PVP K30	18.0 mg	(2.47%)
microcrystalline cellulose	60.0 mg	(8.23%)
PVP CL	30.0 mg	(4.11%)
magnesium stearate	3.5 mg	(0.48%)
colloidal silica	3.5 mg	(0.48%)

metacrylic acid copolymer	9.2 mg	(1.26%)
titanium dioxide	3.3 mg	(0.45%)
polysorbate 80	1.8 mg	(0.25%)
total weight	729.3 mg	

Example 21

The tablets prepared as described in example 4 were coated with a mixture of polyvinylalcohol, titanium dioxide, talc, soya lecithin and xanthan gum, commercially available as Opadry OY-B-28920.

The mixture was suspended in water and sprayed into a coating pan. The resultant film-coated tablets (12 mm diameter) have the following composition expressed as mg/tablet (% by weight):

NAC	600.0 mg	(80.7%)
PVP K30	18.0 mg	(2.42%)
PVP CL	30.0 mg	(4.03%)
microcrystalline cellulose	60.0 mg	(8.06%)
colloidal silica	3.5 mg	(0.47%)
magnesium stearate	3.5 mg	(0.47%)
Opadry OY-B-28920	28.6 mg	(3.85%)
total weight	743.6 mg	

Example 22

The tablets prepared as described in example 14 were coated with a mixture of polyvinylalcohol, titanium dioxide, talc, soya lecithin and xanthan gum, commercially available as Opadry OY-B-28920.

The mixture was suspended in water and sprayed into a coating pan. The resultant film-coated tablets (12 mm diameter) have the following composition expressed as mg/tablet (% by weight):

NAC	600.0 mg	(80.0%)
PVP K30	18.0 mg	(2.4%)
PEG 6000	6.0 mg	(0.8%)

PVP CL	30.0 mg	(4.0%)
microcrystalline cellulose	60.0 mg	(8.0%)
colloidal silica	3.5 mg	(0.47%)
magnesium stearate	3.5 mg	(0.47%)
Opadry OY-B-28920	28.84 mg	(3.86%)
total weight	749.84 mg	

Example 23

The tablets prepared as described in example 15 were coated with a mixture of polyvinylalcohol, titanium dioxide, talc, soya lecithin and xanthan gum, commercially available as Opadry OY-B-28920.

The mixture was suspended in water and sprayed into a coating pan. The resultant film-coated tablets (10 mm diameter) have the following composition expressed as mg/tablet (% by weight):

NAC	400.0 mg	(80.0%)
PVP K30	12.0 mg	(2.4%)
PEG 6000	4.0 mg	(0.8%)
PVP CL	20.0 mg	(4.0%)
microcrystalline cellulose	40.0 mg	(8.0%)
colloidal silica	2.33 mg	(0.47%)
magnesium stearate	2.33 mg	(0.47%)
Opadry OY-B-28920	19.24 mg	(3.86%)
total weight	499.9 mg	

Example 24

The tablets prepared as described in example 16 were coated with a mixture of polyvinylalcohol, titanium dioxide, talc, soya lecithin and xanthan gum, commercially available as Opadry OY-B-28920.

The mixture was suspended in water and sprayed into a coating pan. The resultant film-coated tablets (8 mm diameter) have the following composition expressed as mg/tablet (% by weight):

NAC	200.0 mg	(80.0%)
PVP K30	6.0 mg	(2.4%)
PEG 6000	2.0 mg	(0.8%)
PVP CL	10.0 mg	(4.0%)
microcrystalline cellulose	20.0 mg	(8.0%)
colloidal silica	1.16 mg	(0.47%)
magnesium stearate	1.16 mg	(0.47%)
Opadry OY-B-28920	9.58 mg	(3.86%)
total weight	249.9 mg	

Example 25

The tablets prepared as described in example 17 were coated with a mixture of polyvinylalcohol, titanium dioxide, talc, soya lecithin and xanthan gum, commercially available as Opadry OY-B-28920.

The mixture was suspended in water and sprayed into a coating pan. The resultant film-coated tablets (10 mm diameter) have the following composition expressed as mg/tablet (% by weight):

NAC	400.0 mg	(80.7%)
PVP K30	12.0 mg	(2.42%)
PVP CL	20.0 mg	(4.03%)
microcrystalline cellulose	40.0 mg	(8.06%)
colloidal silica	2.33 mg	(0.47%)
magnesium stearate	2.33 mg	(0.47%)
Opadry OY-B-28920	19.04 mg	(3.85%)
total weight	495.7 mg	

Example 26

The tablets prepared as described in example 18 were coated with a mixture of polyvinylalcohol, titanium dioxide, talc, soya lecithin and xanthan gum, commercially available as Opadry OY-B-28920.

The mixture was suspended in water and sprayed into a coating pan. The resultant film-

coated tablets (8 mm diameter) have the following composition expressed as mg/tablet (% by weight):

NAC	200.0 mg	(80.7%)
PVP K30	6.0 mg	(2.42%)
PVP CL	10.0 mg	(4.03%)
microcrystalline cellulose	20.0 mg	(8.06%)
colloidal silica	1.16 mg	(0.47%)
magnesium stearate	1.16 mg	(0.47%)
Opadry OY-B-28920	9.53 mg	(3.85%)
total weight	247.85 mg	

Example 27

The tablets prepared as described in example 4 were coated with a mixture of polyvinylalcohol, titanium dioxide, talc, soya lecithin and xanthan gum, commercially available as Opadry OY-B-28920, added with sodium saccharin.

The mixture was suspended in water and sprayed into a coating pan. The resultant film-coated tablets have the following composition expressed as mg/tablet (% by weight):

NAC	600.0 mg	(80.6%)
PVP K30	18.0 mg	(2.4%)
PVP CL	30.0 mg	(4.0%)
microcrystalline cellulose	60.0 mg	(8.0%)
colloidal silica	3.5 mg	(0.5%)
magnesium stearate	3.5 mg	(0.5%)
Opadry OY-B-28920	28.6 mg	(3.8%)
sodium saccharin	1.4 mg	(0.2%)
total weight	745 mg	

By working in a similar way, tablets having a lower content of sodium saccharin in the film-coating mixture, 1.0 mg and 0.5 mg respectively, were prepared.

Claims

1) A swallowable tablet containing 80-95% N-acetylcysteine by weight, 0.5-4% by weight with respect to N-acetylcysteine of a binder and further pharmaceutically acceptable excipients.

2) A swallowable tablet according to claim 1 containing 80-95% N-acetylcysteine by weight, 1-3% binder by weight, 2.5-14% diluent by weight, 1-4.5% disintegrant by weight, 0.1-1.5% lubricant by weight optionally in the presence of a flowing agent and of a film-coating layer.

3) A swallowable tablet according to claim 1 or 2 containing 80-90% N-acetylcysteine by weight, 2-3% binder by weight, 3-14% diluent by weight, 1-4.5% disintegrant by weight, 0.1-1% lubricant by weight, 0.1-1% flowing agent and optionally a film-coating layer equal to or lower than 4% by weight.

4) A tablet according to one of the preceding claims wherein the binder is selected among linear polyvinylpyrrolidone, sodium carboxymethylcellulose, ethylcellulose, methylcellulose, liquid glucose, gelatine and hydroxypropylcellulose.

5) A tablet according to claim 4 wherein the binder is linear polyvinylpirrolidone.

6) A tablet according to one of the preceding claims wherein the lubricant is selected among magnesium stearate, sodium stearyl fumarate, sodium benzoate and polyethylene glycol.

7) A tablet according to claim 6 wherein the lubricant is magnesium stearate.

8) A tablet according to one of the preceding claims wherein the diluent is selected among carbohydrates, microcrystalline cellulose and derivatives thereof, inorganic salts, polyalcohols, and mixtures thereof.

9) A tablet according to claim 8 wherein the diluent is microcrystalline cellulose, its derivatives or mixtures thereof.

10) A tablet according to one of the preceding claims wherein the disintegrant is selected among cross-linked polyvinylpyrrolidone, sodium croscarmellose, sodium carboxymethyl starch, starch, pregelatinized starch and microcrystalline cellulose.

11) A tablet according to claim 10 wherein the disintegrant is cross-linked

polyvinylpyrrolidone or sodium croscarmellose.

12) A tablet according to one of the preceding claims containing colloidal silica as flowing agent.

13) A process for the preparation of a swallowable tablet according to one of the preceding claims which comprises the wet granulation of N-acetylcysteine with a binder and optionally all or a part of the estimated amount of diluent, the mixing of the granulate with the remaining excipients, the compression and the optional film-coating of the tablet.

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/EP 00/02464

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/198 A61K9/20 A61K9/36

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 35452 A (ADCOCK INGRAM LIMITED) 14 November 1996 (1996-11-14) page 5; example 2 ---	1-3,6-12
Y	EP 0 315 249 A (MERCK & CO. INC.) 10 May 1989 (1989-05-10) the whole document ---	1-3,6-12
A	EP 0 481 294 A (SPIRIG AG PHARMAZEUTISCHE PRÄPARATE) 22 April 1992 (1992-04-22) the whole document & US 5 401 514 A 28 March 1995 (1995-03-28) cited in the application -----	1-13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 August 2000	24/08/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Benz, K

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ional Application No
PCT/EP 00/02464

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DERWENT-ACC-NO: 2000-664955

DERWENT-WEEK: 200612

TITLE: New tablets achieve higher N-acetylcysteine content than in prior art

INVENTOR: BARINA, R; CASTEGINI, F ; GRASSANO, A ; GURRIERI, G ; ZULIANI, I ; CASTEGININ, F

PATENT-ASSIGNEE: ZAMBON GROUP SPA[ZAMB]

PRIORITY-DATA: 1999IT-MI00704 (April 6, 1999)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
CN 1159004 C	July 28, 2004	N/A	000	A61K 031/198
WO 200059500 A1	October 12, 2000	E	021	A61K 031/198
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EP 1165065 A1	January 2, 2002	E	000	A61K 031/198
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IT 1311907 B	March 20, 2002	N/A	000	A61K 000/00
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DE 60002570 E	June 12, 2003	N/A	000	A61K 031/198
ES 2197087 T3	January 1, 2004	N/A	000	A61K 031/198

DESIGNATED-STATES: AU BR CA CN HU IL JP MX NZ US ZA AT BE CH CY DE DK EA ES FI FR GB GR IE IT LU MC NL PT SE AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU M C NL PT SE SI

APPLICATION-DATA:

PUB-NO	APPL-DESCRIPTOR	APPL-NO	APPL-DATE
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DE 60002570E	Based on	EP 1165065	N/A
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ES 2197087T3	N/A	2000EP-0920520	March 21, 2000

ES 2197087T3	Based on	EP 1165065	N/A

INT-CL (IPC): A61K000/00, A61K009/20 , A61K009/36 , A61K031/198 , A61P011/10 , A61P011/12

ABSTRACTED-PUB-NO: WO 200059500A

BASIC-ABSTRACT:

NOVELTY - Swallowable tablets containing N-acetylcysteine (80-95 wt.%), a binder (0.5-4 wt.%) and excipients, are new.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for the preparation of the tablets by wet granulation of N-acetylcysteine with a binder and optionally all or part of the estimated amount of diluent, followed by mixing the granulate with the remaining excipients, compression and optionally film-coating the tablets.

ACTIVITY - Mucolytic; expectorant.

USE - N-acetylcysteine is a mucolytic and an expectorant.

ADVANTAGE - The tablets incorporate a high N-acetylcysteine content (80-95%), unlike prior art formulations (generally 50-65%). The tablets show physical characteristics which fulfill the requirements imposed by the Official Pharmacopoeias. Their hardness will generally be 6-14 Kp, the friability 0.05-0.7% and the disintegration time being less than 15 minutes for the no-film coated tablets.

CHOSEN-DRAWING: Dwg.0/0

TITLE-TERMS: NEW TABLET ACHIEVE HIGH N CONTENT PRIOR ART

DERWENT-CLASS: A96 B05

CPI-CODES: A12-V01; B10-C04D; B12-M11B; B14-K01E;

CHEMICAL-CODES: Chemical Indexing M1 *01* Fragmentation Code F012 F013 F423 H7 H715 H721 J5 J521 L9 L941 M210 M212 M240 M281 M320 M423 M431 M510 M521 M530 M540 M782 M904 M905 Q120 R038 Specfic Compounds A00D5K A00D5M

Chemical Indexing M1 *02* Fragmentation Code A111 A960 C710 H5 H521 H8 J0 J011 J1 J171 M280 M311 M321 M342 M349 M381 M391 M423 M431 M630 M782 M904 M905 M910 Q120 R038 Specfic Compounds 07352K 07352M A0GUZK A0GUZM Registry Numbers 1835U

Chemical Indexing M1 *03* Fragmentation Code H5 H521 H8 M210 M212 M272 M281 M320 M423 M431 M782 M904 M905 M910 Q120 R038 Specfic Compounds 01858K 01858M A02KYK A02KYM Registry Numbers 1858U

Chemical Indexing M1 *04* Fragmentation Code H5 H521 H8 M210 M211 M272 M281 M320 M423 M431 M782 M904 M905 M910 Q120 R038 Specfic Compounds 01860K 01860M A02KXK A02KXM Registry Numbers 1860U

Chemical Indexing M1 *05* Fragmentation Code M423 M431 M782 M904 M905 Q120 R038 Specfic Compounds 24033K 24033M

Chemical Indexing M1 *06* Fragmentation Code H4 H401 H481 H5 H521 H8 M280 M313 M321 M332 M342 M383 M391 M423 M431 M782 M904 M905 Q120 R038 Specfic Compounds 03005K 03005M

Chemical Indexing M2 *07* Fragmentation Code H4 H498 H9 J0 J012 J1 J171 J3 J371 M210 M211 M262 M281 M312 M321 M332 M343 M349 M381 M391 M416 M431 M620 M782 M904 M905 P823 Q120 R038 Specfic Compounds 04369K 04369T 04369M

Chemical Indexing M2 *08* Fragmentation Code H4 H405 H484 H8 J4 J471 K0 L8 L814 L821 L831 M280 M315 M321 M332 M344 M349 M381 M391 M416 M431 M620 M782 M904 M905 M910 Q120 R038 Specfic Compounds 00038K 00038M

Chemical Indexing M6 *09* Fragmentation Code M905 P823 Q120 R038 R111 R280 R303 R304 R307 R308 R312

UNLINKED-DERWENT-REGISTRY-NUMBERS: ; 1835U ; 1858U ; 1860U

ENHANCED-POLYMER-INDEXING: Polymer Index [1.1] 018 ; G0635 G0022 D01 D12 D10 D23 D22 D31 D41 D51 D53 D58 D75 D86 F71 ; H0000

Polymer Index [1.2] 018 ; R07352 R06717 G3678 G3634 G3623 D01 D03 D11 D10 D23 D22 D31 D42 D50 D61 D76 D92 F24 F34 F38 F35 Na 1A H0293 P0599 ; R01858 G3678 G3634 D01 D03 D11 D10 D23 D22 D31 D42 D50 D76 D92 F24 F34 H0293 P0599 G3623 ; R01860 G3678 G3634 D01 D03 D11 D10 D23 D22 D31 D42 D50 D76 D89 F24 F34 H0293 P0599 G3623 ; R24033 G3714 P0599 D01 F70 ;

R03005 G3678 G3634 D01 D03 D11 D10 D23 D22 D31 D42 D50 D76 D93 F24 F29 F26 F34 H0293 P0599 G3623

Polymer Index [1.3] 018 ; Q9999 Q6791 ; Q9999 Q8037 Q7987 ; ND01 ; B9999 B3792 B3747 ; B9999 B3781 B3747

Polymer Index [2.1] 018 ; R00351 G1558 D01 D23 D22 D31 D42 D50 D73 D82 F47 ; P8004 P0975 P0964 D01 D10 D11 D50 D82 F34 ; P0055 ; H0000

Polymer Index [2.2] 018 ; Q9999 Q8037 Q7987 ; ND01 ; B9999 B3792 B3747 ; B9999 B3781 B3747 ; Q9999 Q7841 ; B9999 B5094 B4977 B4740

Polymer Index [3.1] 018 ; R01852*R G3634 D01 D03 D11 D10 D23 D22 D31 D42 D50 D76 D86 F24 F29 F26 F34 H0293 P0599 G3623

Polymer Index [3.2] 018 ; Q9999 Q8037 Q7987 ; ND01 ; B9999 B3792 B3747 ; B9999 B3781 B3747

Polymer Index [4.1] 018 ; G0635 G0022 D01 D12 D10 D23 D22 D31 D41 D51 D53 D58 D75 D86 F71 ; H0000 ; M9999 M2073

Polymer Index [4.2] 018 ; R01852*R G3634 D01 D03 D11 D10 D23 D22 D31 D42 D50 D76 D86 F24 F29 F26 F34 H0293 P0599 G3623

Polymer Index [4.3] 018 ; Q9999 Q8037 Q7987 ; ND01 ; B9999 B3792 B3747 ; B9999 B3781 B3747

Polymer Index [5.1] 018 ; R01863*R D01 D11 D10 D23 D22 D31 D42 D50 D76 D86 F24 F29 F26 F34 H0293 P0599 G3623 ; M9999 M2200 ; M9999 M2062 ; M9999 M2379*R ; M9999 M2415

Polymer Index [5.2] 018 ; Q9999 Q8037 Q7987 ; ND01 ; B9999 B3792 B3747 ; B9999 B3781 B3747

Polymer Index [5.3] 018 ; Na 1A ; H0157

SECONDARY-ACC-NO:

CPI Secondary Accession Numbers: C2000-201413